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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,677	03/19/2007	Allen Rosenspire	66174-0006	4698

10291 7590 10/06/2009

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	

MAIL DATE	DELIVERY MODE
10/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,677	ROSENSPIRE ET AL.	
	Examiner	Art Unit	
	SUSAN E. FERNANDEZ	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-43 are pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-14, 16-18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kindzelskii et al. (Biochimica et Biophysica Acta. 2000. 1495: 90-111) in light of the Journal of Cell Science (2001. 114: 1515-1520).

Kindzelskii et al. discloses that "…external pulsed DC electric fields phase-matched to endogenous cellular oscillations lead to enhanced metabolic oscillations or metabolic resonance and cell extension" (page 91, first column, last paragraph). Furthermore, "metabolic resonance is accompanied by exaggerated cell extension" (page 97, first column, last paragraph). Kindzelskii et al. found that "phase-matched electric fields induce metabolic resonance in cells and greatly exaggerate cell extension or shape change" (page 99, first paragraph). As the electric fields are phase matched to the endogenous cellular oscillations, the electric field has a frequency within 10% of the frequency of the internal NAD(P)H oscillation frequency within the cells, thus meeting limitations in instant claim 11.

It is noted that electric fields applied at NAD(P)H autofluorescence troughs trigger metabolic resonance and enhance spreading, whereas electric fields applied at NAD(P)H

autofluorescence crests disrupt oscillations and the spreading of nascent pseudopods (page 103, first paragraph). Metabolic resonance is exhibited by NAD(P)H autofluorescence oscillations that grow in amplitude (page 94, last paragraph and Figure 10 on page 101, where magnetic resonance is triggered for electric fields of 2 $x10^{3}$ V/m to 1 x 10^{-4} V/m which meets the requirements of instant claims 12 and 13). See also Figure 4, which indicates that "When an electric field (arrows) is applied at NAD(P)H autofluorescence troughs, the metabolic oscillations increase in amplitude, illustrating metabolic resonance, in the absence and presence of FMLP (e, f)."

The electric fields can also be applied at the NAD(P)H autofluorescence crests (page 103, first column). It can be seen from Figure 13 that the spreading neutrophils become spherical after exposure to such an electric field (see (C) and (D)). Therefore, there is also a change in neutrophil shape. Further still, the electric field is applied at other than the minima of the NAD(P)H oscillation frequency and at the oscillation crests, thus meeting the requirements of instant claims 14, 17, and 18.

It is also noted that the Kindzelskii study is performed on neutrophils isolated from the peripheral blood of normal healthy adults (page 91, second column, first full paragraph). Furthermore, the pulsed DC field is applied on migrating cells (page 94, second column, last paragraph). As pointed out in the Journal of Cell Science, cells assuming polarized morphology are migratory (page 1516, second column, second full paragraph). Therefore, the application of electric fields of the Kindzelskii study is performed on polarized cells.

A holding of anticipation is clearly required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenpire et al. (Biophysical Journal. 2000. 79(6): 3001-3008) in view of Kindzelskii et al. (Biochimica et Biophysica Acta. 2000. 1495: 90-111) and Gordon (US 4,758,429).

Rosenpire et al. discloses monitoring NAD(P)H autofluorescence in spherical and polarized neutrophils (page 3001, second to last paragraph and Figure 1), where the neutrophils are purified from the blood of healthy individuals (page 3001, second column, second paragraph). The reactive oxygen metabolite (ROM) production, an important neutrophil effector function, is controlled by NAD(P)H metabolic oscillation (page 3001, first column). Electric fields of square-wave voltage forms were applied, as well as electric fields of sinusoidal voltage

forms (page 3001, last paragraph). Figure 6 shows the effects of electric fields generated by a series of three properly phase- and frequency-matched sinusoidal voltage forms which have sequentially established resonance with NAD(P)H oscillations in an adherent neutrophil (page 3005, first full paragraph). Clearly, the electric field has a frequency within about 10% of the frequency of internal NAD(P)H oscillations with the cell, and is applied for a time period equal to three periods of NAD(P)H oscillation, thus meeting limitations in instant claims 2, 4, 5, 11. The adherent neutrophils are polarized cells (page 3003, first paragraph). It is pointed out in Figure 6 that "initial application of the AC voltage was begun at a NAD(P)H minimum" and that the "AC electric fields resonate with naturally occurring NAD(P)H oscillations in human neutrophils." From Figure 6, it is clear that the amplitudes of NAD(P)H oscillations increase when the electric field in sinusoidal AC voltage form is applied. Electric field strengths applied include 9.0×10^{-2}, 4.5×10^{-1}, and 2.3 V/m (Figure 6), thus meeting limitations in instant claims 3, 12, 13.

Rosenpire et al. does not expressly disclose that the shape of the converted polarized eukaryotic cells is converted.

Kindzelskii et al. discloses that "…external pulsed DC electric fields phase-matched to endogenous cellular oscillations lead to enhanced metabolic oscillations or metabolic resonance and cell extension" (page 91, first column, last paragraph). Furthermore, "metabolic resonance is accompanied by exaggerated cell extension" (page 97, first column, last paragraph). Kindzelskii et al. found that "phase-matched electric fields induce metabolic resonance in cells and greatly exaggerate cell extension or shape change" (page 99, first paragraph). It is noted that electric fields applied at NAD(P)H autofluorescence troughs trigger metabolic resonance and enhance

spreading, whereas electric fields applied at NAD(P)H autofluorescence crests disrupt oscillations and the spreading of nascent pseudopods (page 103, first paragraph). Metabolic resonance is exhibited by NAD(P)H autofluorescence oscillations that grow in amplitude (page 94, last paragraph and Figure 10, where magnetic resonance is triggered for electric fields of 2 $x10^{3}$ V/m to 1 x 10^{-4} V/m). The electric fields can also be applied at the NAD(P)H autofluorescence crests (page 103, first column). It can be seen from Figure 13 that the spreading neutrophils become spherical after exposure to such an electric field (see (C) and (D)). Therefore, there is also a change in neutrophil shape. Further still, the electric field is applied at other than the minima of the NAD(P)H oscillation frequency and at the oscillation crests, thus meeting the requirements of instant claims 14, 17, and 18. Kindzelskii et al. indicates that "…by manipulating the phase differences between the applied electric field and a cell's endogenous metabolic oscillations, one can affect the production of oxidants in parallel with cytoskeletal assembly and NAD(P)H amplitudes" (page 104, first column, first paragraph).

It would have been obvious that the electric fields of sinusoidal voltage forms applied to the polarized (adherent) cells as taught in Rosenpire et al. would have resulted in a change in cell shape. A change in cell shape would have occurred since in Figure 6 of Rosenpire et al., it is clear that the amplitudes of NAD(P)H oscillations increase when the electric field in sinusoidal AC voltage form is applied. As pointed out in Kindzelskii et al., metabolic resonance is exhibited by NAD(P)H autofluorescence osciallations that grow in amplitude, and a showing of metabolic resonance is accompanied by exaggerated cell extension, and hence a change in cell shape.

Further still, Rosenpire et al. differs from the claims in that it does not teach that the electric field is applied at other than the minima of the NAD(P)H oscillation frequency. At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have modified the Rosenpire invention such that the electric fields of sinusoidal voltage forms are applied to the polarized cells at the NAD(P)H oscillation crests. One of ordinary skill in the art would have been motivated to do this since in order to control the reactive oxygen metabolite (ROM) production in another manner. Kindzelskii demonstrates that when an electric field is applied to neutrophils out-of-phase, such as in the application at the oscillation crests performed in its study, oxidant production ceases (page 104, Figure 14). Therefore, there would have been a reasonable expectation of success that applying the sinusoidal electric fields would have ceased ROM production in the Rosenpire invention. Thus, claims 14, 17, and 18 are rendered obvious.

Finally, the references differ from the claimed invention in that they do not teach that the electric field is applied by means of magnetic induction. However, electromagnetic field is a known means for applying an electric field to cells. See Gordon, claim 1. The application of an electromagnetic field entails application of an electric field by means of magnetic induction. It would have been obvious to the person of ordinary skill in the art to have used an electromagnetic field since the electromagnetic field provides an electric field as required by Rosenpire et al. Thus, claims 6, 15, and 19 are rendered obvious. Furthermore, it would have been a matter of routine experimentation to have varied that pulse trains of the magnetic induction. Thus, claims 38-41 are rendered obvious.

Claims 21, 22, 24-26 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon (US 4,758,429).

Gordon discloses a process for the treatment of arthritis (an inflammatory, pathological condition in mammals) wherein a relatively low frequency alternating, oscillating and/or pulsed electromagnetic field is provided to the joint space (claim 1). The application of an electromagnetic field entails application of an electric field by means of magnetic induction.

Gordon does not expressly disclose that the electric field applied to the tissue is at least 10^{-2} V/m or at least 10^{-5} V/m. However, the selection of a suitable field strength would have been a matter of routine experimentation on the part of the skilled artisan.

A holding of obviousness is clearly required.

Claims 21-37, 42, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon in view of Litovitz (US 5,968,527).

As discussed above, Gordon renders claims 21, 22, 24-26, and 31 obvious. However, it does not expressly disclose that a coil applicator is used, or that the magnetic induction comprises a time-varying magnetic field in square wave and sawtooth wave forms.

Litovitz discloses using time-varying fields, such as electric and magnetic fields, on organs (column 7, lines 54-60). The periodic signals emitted may be triangular waves, square waves, and pulse trains (column 15, lines 6-9). Moreover, a coil applicator may be used (column 14, lines 31-38).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have used time-varying fields with square and sawtooth wave forms (for the

magnetic field) and to have used a coil applicatior when practicing the Gordon invention. One of ordinary skill in the art would have been motivated to do this since there would have been a reasonable expectation of success of changing these features of the Gordon invention to still obtain an effect on tissue. These features still would have been suitable for obtaining an electromagnetic field as required by the Gordon invention. Thus, claims 23, 27-30, and 32-37 are rendered obvious. Furthermore, in the practice of the Gordon invention, polarized eukaryotic cells would have been amongst the joint cells. It would have been obvious to have varied pulse trains through routine experimentation. Thus, claims 42 and 43 are rendered obvious.

A holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN E. FERNANDEZ whose telephone number is (571)272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Susan E. Fernandez
Examiner
Art Unit 1651

sef